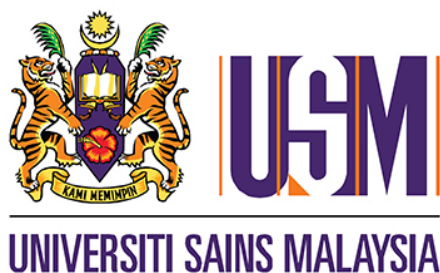


**THE IMPACT OF CRANIOPLASTY ON CEREBRAL BLOOD FLOW
AND ITS CORRELATION WITH CLINICAL OUTCOME IN PATIENTS
UNDERWENT DECOMPRESSIVE CRANIECTOMY**

BY

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CONTENTS

Title	Page
Acknowledgement	ii
Contents	iv
List of tables and figures	vi
List of abbreviations	xi
Abstract [Bahasa Malaysia]	xii
Abstract [English]	xvi
1. Introduction	1
2. Literature Review	6
3. Objectives	16
4. Research Methodology	18
4.1 Study design	18
4.2 Reference and source population	18
4.3 Sampling frame and data collection	18
4.4 Selection criteria	19
4.5 Study schedule	20
4.6 Study procedure and evaluations	21
4.7 Clinical assessment and data management	28
4.8 Assessment of safety	28
4.9 Surgical technique	30
4.10 Handling of withdrawals	30
4.11 Termination of study	30

4.12 Sample size calculation	31
4.13 Definition of variables	32
4.14 Study flow chart	34
5. Results	35
5.1 Descriptive analysis	35
5.2 CT perfusion findings	37
5.3 Clinical findings	41
5.4 CT perfusion and clinical outcome	55
6. Discussion	56
7. Conclusion	70
8. Limitation of study	72
9. Appendix	74
10. References	81

LIST OF TABLES

Table	Page
Table 4.1 CT Technical Protocol	26
Table 4.2 Category of contrast related reactions	28
Table 5.1 Demographic analysis	36
Table 5.2 Descriptive statistics of cerebral blood flow (CBF) for ipsilateral and contralateral hemisphere for pre-cranioplasty and 6 weeks post cranioplasty	37
Table 5.3 Non-Parametric Wilcoxon Signed-Rank Test (Median value of cerebral blood flow (CBF) for ipsilateral and contralateral hemisphere at pre-cranioplasty and 6 weeks post-cranioplasty)	39
Table 5.4 Fischer Exact Test for types of cranioplasty and ipsilateral cerebral blood flow (CBF) at pre-cranioplasty and 6 weeks post-cranioplasty	40
Table 5.5 Fischer Exact Test for types of cranioplasty and contralateral cerebral blood flow (CBF) at pre-cranioplasty and 6 weeks post-cranioplasty	40
Table 5.6 Descriptive statistics of Glasgow outcome score (GOS) at pre-cranioplasty, 6 weeks and 24 weeks post-cranioplasty	41
Table 5.7 Non-Parametric Wilcoxon Signed-Rank Test (Median value of Glasgow outcome score (GOS) at pre–cranioplasty and 6 weeks post-cranioplasty)	45
Table 5.8 Non-Parametric Wilcoxon Signed-Rank Test (Median value of Glasgow outcome score (GOS) at pre–cranioplasty and 24 weeks post-	45

cranioplasty)	
Table 5.9 Non-Parametric Wilcoxon Signed-Rank Test (Median value of Glasgow outcome score (GOS) at 6 weeks post –cranioplasty and 24 weeks post-cranioplasty)	45
Table 5.10 Descriptive statistics of Mini Mental State Examination (MMSE) at pre-cranioplasty, 6 weeks and 24 weeks post-cranioplasty	46
Table 5.11 Non-Parametric Wilcoxon Signed-Rank Test (Median value of Mini mental state examination (MMSE) at pre –cranioplasty and 6 weeks post-cranioplasty)	50
Table 5.12 Non-Parametric Wilcoxon Signed-Rank Test (Median value of Mini mental state examination (MMSE) at pre –cranioplasty and 24 weeks post-cranioplasty)	50
Table 5.13 Non-Parametric Wilcoxon Signed-Rank Test (Median value of Mini mental state examination (MMSE) at 6 weeks post –cranioplasty and 24 weeks post-cranioplasty)	50
Table 5.14 Descriptive statistics of Frontal Assessment Battery (FAB) at pre-cranioplasty, 6 weeks and 24 weeks post-cranioplasty	51
Table 5.15 Non-Parametric Wilcoxon Signed-Rank Test (Median value of Frontal assessment battery (FAB) at pre–cranioplasty and 6 weeks post-cranioplasty)	53
Table 5.16 Non-Parametric Wilcoxon Signed-Rank Test (Median value of Frontal assessment battery (FAB) at pre–cranioplasty and 6 weeks post-cranioplasty)	53

Table 5.17 Non-Parametric Wilcoxon Signed-Rank Test (Median value of Frontal assessment battery (FAB) at 6 weeks post–cranioplasty and 24 weeks post-cranioplasty	53
Table 5.18 Non-Parametric Spearman’s Correlation Test (Cerebral Blood Flow (CBF) & Clinical Outcome) at 6 Weeks Post-Cranioplasty	55

LIST OF FIGURES

Figure	Page
Figure 4.1 (a,b) Patient undergoing CTP analysis performed using 40-slice CT scanner (SIEMENS, SOMATOM Sensation Open)	23
Figure 4.2 (a) 40-detector row scan (SIEMENS, SOMATOM Sensation Open) (b) Non-ionic contrast Iopamidol (Bracco, Iopamiro 370)	24
Figure 4.3 Baseline source and averaged CT perfusion image (CBF) map pre-cranioplasty and 6 weeks post-cranioplasty in one of our patient.	25
Figure 5.1 Box plot of cerebral blood flow (CBF) for ipsilateral and contralateral hemisphere at pre-cranioplasty and 6 weeks post-cranioplasty	38
Figure 5.2 Box plot of Glasgow outcome score (GOS) at pre-cranioplasty, 6 weeks and 24 weeks post-cranioplasty	42
Figure 5.3 The distribution of Glasgow outcome score (GOS) based on good and poor outcome at pre-cranioplasty	43
Figure 5.4 The distribution of Glasgow outcome score (GOS) based on good and poor outcome at 6 weeks post-cranioplasty	43
Figure 5.5 The distribution of Glasgow outcome score (GOS) based on good and poor outcome at 24 weeks post-cranioplasty	44
Figure 5.6 Box plot of Mini mental state examination (MMSE) at pre-cranioplasty, 6 weeks and 24 weeks post-cranioplasty	47
Figure 5.7 The distribution of Mini mental state examination (MMSE) based on normal, mild, moderate and severe cognition impairment at pre-cranioplasty	48

- Figure 5.8 The distribution of Mini mental state examination (MMSE) based on normal, mild, moderate and severe cognition impairment at 6 weeks post-cranioplasty. 48
- Figure 5.9 The distribution of Mini mental state examination (MMSE) based on normal, mild, moderate and severe cognition impairment at 24 weeks post-cranioplasty 49
- Figure 5.10 Box plot of Frontal Assessment Battery (FAB) at pre-cranioplasty, 6 weeks and 24 weeks post-cranioplasty. 52

LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
CBF	Cerebral blood flow (ml/min/100g)
CONT	Contralateral
CT perfusion	Computed tomography perfusion
DC	Decompressive craniectomy
FAB	Frontal assessment battery
GOS	Glasgow outcome score
GOSE	Extended glasgow outcome score
IPSI	Ipsilateral
IQR	Interquartile range
MMSE	Mini mental state examination scores
ROI	Region of interest
SSSF	Syndrome of sinking skin flap syndrome
ST	Syndrome of trephined

ABSTRAK (BAHASA MALAYSIA)

Topik

IMPAK KRANIOPLASTI PADA PENGALIRAN DARAH SEREBRUM DAN HUBUNGANNYA DENGAN HASIL KEPUTUSAN KLINIKAL KEATAS PESAKIT YANG PERNAH MENJALANI PEMBEDAHAN DIKOMPRESI KRANIEKTOMI

Latar belakang

Dikompresi kraniektomi kerap dijalankan keatas pesakit yang mempunyai hipertensi otak yang gagal dirawat secara perubatan. Adalah amalan biasa di Malaysia dan seluruh dunia, pesakit yang pernah menjalani dikompresi kraniektomi akan menjalani pembedahan kranioplasti. Peningkatan hasil keputusan klinikal telah diperhatikan di antara pesakit yang menjalani kranioplasti. Pemulihan pengaliran darah serebrum telah dinyatakan sebagai salah satu factor yang menyebabkan peningkatan hasil keputusan klinikal selepas kranioplasti. Oleh yang demikian, kajian ini dijalankan untuk menentukan impak kranioplasti terhadap pengaliran darah serebrum dan hubungannya dengan hasil keputusan klinikal keatas pesakit yang pernah menjalani pembedahan dikompresi kraniektomi.

Objektif

Tujuan kajian ini adalah untuk menilai pengaruh kranioplasti terhadap pengaliran darah serebrum dengan menggunakan CT perfusi pada pesakit yang pernah menjalani pembedahan dikompresi kraniektomi. Selain itu, impak kranioplasti terhadap hasil keputusan klinikal berdasarkan GOS, MMSE dan FAB turut dinilai. Seterusnya, ini membolehkan hubungan antara pengaliran darah serebrum dan hasil keputusan klinikal dinilai.

Kaedah Kajian

Kajian ini adalah kajian prospektif secara pemerhatian dikalangan pesakit yang telah menjalani pembedahan dekompresi kraniektomi untuk tujuan hipertensi otak dan memerlukan pembedahan kranioplasti di Hospital Sungai Buloh. Kajian ini dijalankan dari 1hb September 2013 sehingga 1hb September 2014 di mana seramai 22 pesakit terlibat dalam kajian ini. Kesemua pesakit akan menjalani CT perfusi untuk menentukan nilai pengaliran darah serebrum semasa kemasukan ke wad untuk kranioplasti. Selain itu, hasil keputusan klinikal turut akan diuji menggunakan skala GOS, MMSE dan FAB. Rawatan susulan adalah pada 6 dan 24 minggu selepas kranioplasti. CT perfusi dan pemeriksaan keputusan klinikal dijalankan pada rawatan susulan 6 minggu selepas kranioplasti, manakala hanya pemeriksaan keputusan klinikal dijalankan pada rawatan susulan 24 minggu selepas kranioplasti. Keputusan dan data dalam kajian ini dianalisa dengan menggunakan aplikasi SPSS versi 12.0.1.

Keputusan

Nilai median pengaliran darah serebrum pada sebelah ipsilateral sebelum kranioplasti adalah 48.87 (IQR 25.05) ml/min/100g dan bertambah kepada 61.10 (IQR 31.65) ml/min/100g 6 minggu selepas kranioplasti. Perbezaan ini adalah terbukti secara statistik dengan nilai $p < 0.001$. Pada sebelah kontralateral, nilai median pengaliran darah sebelum kranioplasti adalah 60.55 (IQR 23.61) ml/min/100g dan telah bertambah kepada 71.84 (IQR 24.59) ml/min/100g 6 minggu selepas kranioplasti, dengan nilai $p < 0.001$. Nilai median GOS adalah 4, sebelum kranioplasti, 6 dan 24 minggu selepas kranioplasti. Nilai median yang sama ini, adalah terbukti secara statistik sebelum kranioplasti kepada 6 dan 24 minggu selepas kranioplasti dengan nilai $p = 0.046$ dan $p = 0.014$ masing-masing. Mini mental state examination (MMSE) pula menunjukkan nilai

median 22 (IQR 12.75) sebelum kranioplasti, 25 (IQR 12.50) 6 minggu selepas kranioplasti dan 25.5 (IQR 13.00) 24 minggu selepas kranioplasti. Perbezaan nilai median MMSE sebelum kranioplasti kepada 6 dan 24 minggu selepas kranioplasti adalah terbukti secara statistik dengan nilai $p=0.001$ dan $p<0.001$. Nilai median FAB adalah 12 (IQR 10.75) sebelum kranioplasti, 14.5 (IQR 11.35) 6 minggu selepas kranioplasti dan 15 (IQR 11.25) 24 minggu selepas kranioplasti. Perbezaan nilai median FAB sebelum kranioplasti kepada 6 dan 24 minggu selepas kranioplasti adalah terbukti secara statistic dengan $p=0.002$ dan $p=0.001$ masing-masing. Korelasi diantara pengaliran darah serebrum dan hasil keputusan klinikal adalah tidak signifikan dengan nilai $p>0.05$.

Kesimpulan

Pada masa dahulu, kranioplasti diketahui sebagai pembedahan yang mampu memulih-baikan kecacatan tengkorak untuk memberi perlindungan kepada otak dan nilai cosmesis. Kajian ini, menunjukan kranioplasti memberi peningkatan kepada pengaliran darah serebrum pada sebelah ipsilateral dan kontralateral. Selain itu, kami juga mampu membuktikan nilai therapeutik kranioplasti terhadap peningkatan hasil keputusan klinikal dalam kajian ini. Walaupun, kami tidak dapat menunjukan korelasi yang kukuh diantara pengaliran darah serebrum dengan peningkatan hasil keputusan klinikal, kesimpulan hasil kajian kami setakat ini mampu memberikan pedoman awal mengenai peranan penting kranioplasti terhadap peningkatan perfusi otak dan hasil keputusan klinikal. Kami berharap pada masa hadapan, ini akan menjana minat dikalangan saintis untuk menjalankan multi-centered randomized trial dengan melibatkan lebih pesakit, bagi tujuan memperkukuhkan lagi kesimpulan kajian ini. Berdasarkan kesimpulan kajian ini, kami menyarankan agar pembedahan kranioplasti patut disyorkan kepada semua pesakit yang

pernah menjalani dikompresi kraniektomi bagi tujuan meningkatkan pengaliran darah serebrum dan hasil keputusan klinikal, selain mampu memberi perlindungan otak dan nilai cosmesis.

ABSTRACT (ENGLISH)

Title

THE IMPACT OF CRANIOPLASTY ON CEREBRAL BLOOD FLOW AND ITS CORRELATION WITH CLINICAL OUTCOME IN PATIENTS UNDERWENT DECOMPRESSIVE CRANIECTOMY

Background

Decompressive craniectomy are commonly use as the treatment for medically refractory intracranial hypertension. It is a common practice in Malaysia and worldwide, that patient will have subsequent reconstructive cranioplasty. Unexpected improvement in patient's neurological status has been observed among patients that underwent cranioplasty procedure. Restoration of CBF hemodynamics is one of the factors said to affect patient's clinical outcome post-cranioplasty. Therefore, this study was conducted to determine the impact of cranioplasty on CBF and its correlation with clinical outcome in patients undergoing decompressive craniectomy.

Objectives

This study was done to evaluate the effect of cranioplasty on CBF with CT perfusion in patients with previous decompressive craniectomy undergoing cranioplasty. Besides that, the effect of cranioplasty on clinical outcome based on GOS, MMSE & FAB was also evaluated. This study also aimed to determine the correlation between post-cranioplasty CBF and clinical outcome.

Methodology

A prospective observational study was done on patients who have underwent decompressive craniectomy for intracranial hypertension and requiring reconstructive cranioplasty at Hospital Sungai Buloh. This study was conducted between 1st September 2013 and 1st September 2014 and a total of 22 patients were included in this study. During admission, all patients had CT perfusion done to determine pre-cranioplasty CBF. Clinical outcome was assessed using GOS, MMSE and FAB. Subsequent, follow up was done at 6 weeks and 24 weeks post-cranioplasty. At 6 weeks post cranioplasty follow up, a repeat CT perfusion scan and assessment of clinical outcome was performed. During the 24 weeks post-cranioplasty follow up, only clinical outcome was evaluated. Data entry and analysis was done using Statistical Package for Social Sciences (SPSS) version 12.0.1.

Results

The median value of the ipsilateral cortical CBF was 48.87 (IQR 25.05) ml/min/100g and 61.10 (IQR 31.65) ml/min/100g at pre-cranioplasty and 6 weeks post-cranioplasty respectively ($p < 0.001$). Similarly for contralateral cortical CBF, which showed improvement from 60.55 (IQR 23.61) ml/min/100g to 71.84 (IQR 24.59) ml/min/100g at 6 weeks post-cranioplasty ($p < 0.001$). No difference seen in the median value for GOS which was 4 at pre, 6 and 24 weeks post-cranioplasty with $p = 0.046$ and $p = 0.014$ respectively. Median value for MMSE showed significant difference with value of 22 (IQR 12.75), 25 (IQR 12.50) and 25.5 (IQR 13.00) at pre-cranioplasty, 6 and 24 weeks post-cranioplasty respectively ($p = 0.001$ and $p < 0.001$). Median value for FAB was 12 (IQR 10.75) at pre-cranioplasty, 14.5 (IQR 11.35) at 6 weeks post-cranioplasty and 15 (IQR 11.25) at 24 weeks post-cranioplasty. The difference at pre-

cranioplasty to 6 and 24 weeks post-cranioplasty was significant with $p=0.002$ and $p=0.001$ respectively. No significant correlation between CBF and clinical outcome ($p>0.05$).

Conclusion

Cranioplasty in the past is known as a surgical procedure that restore cranial defect to provide cerebral protection and cosmesis. In our present study, it suggests that cranioplasty can remarkably improve cortical perfusion for both the ipsilateral and contralateral hemisphere. Besides that, we also believe that cranioplasty has a therapeutic role in terms of clinical outcome improvement which was observed in our study. Even though, we are unable to establish a strong positive correlation between improved cerebral blood flow and clinical outcome, the results obtained so far may shed light on the significant role of cranioplasty on the improvement of cerebral perfusion and clinical outcome. This we hope will generate interest among future researchers to carry out multi-centered randomized trials which can analyze a larger number of patients to further draw a concrete conclusion to support our claim. Based on this study, we would like to propose that cranioplasty should be done to all patients with previous history of decompressive craniectomy to improve cerebral perfusion and clinical outcome as it also provides cerebral protection and cosmetic correction.

CHAPTER ONE: INTRODUCTION

Decompressive craniectomy procedure has recently experienced a renewed interest among neurosurgeons worldwide. Patients underwent DC have remarkably increased in number over the last few decades, as more studies has shown its effectiveness in reducing mortality rate, by reducing the adverse effects of severe cerebral edema and swelling (Venes and Collins, 1975; Cooper *et al.*, 1976).

Relief of intracranial pressure by DC was first described by Cushing in the early 20th century (Cushing, 1908). Since then surgical decompressive has been advocated as a treatment for severe brain edema associated with brain injury and infarction (Ransohoff *et al.*, 1971). Decompressive craniectomy is described as the removal of an area of skull bone with the objective of converting the ‘closed’ intracranial compartment into an ‘open’ compartment. Current and widely acceptable modalities for the treatment of increased ICP include medical management such as 30-degree head up, sedation, hyperventilation, osmotic diuresis, barbiturate-induced coma and surgical management such as cerebrospinal fluid (CSF) drainage and DC (Honeybul *et al.*, 2010).

Many published articles demonstrated good surgical outcome following cranioplasty, however till today there are no clearly defined indication for, or optimal timing of the procedure (Reddy *et al.*, 2002). Decompressive craniectomy has most commonly been performed in patient with traumatic brain injury and ischemic stroke associated with intractable intracranial hypertension. Other indications, which are less frequently described, include meningitis, subdural empyema, encephalitis, acute disseminated encephalomyelitis and cerebral venous and dural sinus thrombosis.

Decompressive craniectomy if performed early, has been shown to reduce mortality, improves functional recovery, reduces the duration of stay in intensive care unit and improves Barthel Index Score(Kunze *et al.*, 1998). These effects are thought to be due to improved collateral circulation, reduction in tissue edema and improvement in oxygenation and energy metabolism in injured tissues (Zweckberger *et al.*, 2003).

Decompressive craniectomy is not without its own morbidity. In some studies it has been reported as much as 50% complication rate postoperatively (Yang *et al.*, 2008). A very important drawback of DC is the increased risk of brain injury. Honeybul reports a case of a middle-aged man who had DC following traumatic brain injury as a result of fall. The patient was making good recovery when he unfortunately fell a second time on the unprotected craniectomy site. As a consequence, he succumbed to the injury (Honeybul, 2009). This case highlights the need for reconstructive cranioplasty after decompressive craniectomy for cerebral protection. Besides that, patient who undergoes DC will subsequently require cranioplasty resulting in the need for 2 surgeries, the first being the removal of the bone flap and the second to repair the defect (cranioplasty). This is also a potential cause of concern since cranioplasty has also been associated with a number of known surgical and anesthetic complications.

One particular major complication that has been associated with DC is the syndrome of sinking skin flap (SSSF) described by Yamaura and Makino (Yamaura and Makino, 1977) . The SSSF is characterized by neurological symptoms (headache, epileptic seizures, vertigo, dysesthesias, or paresis) which develop over weeks to months after large a DC. There are also few reports of a syndrome characterized by subjective symptoms such as headache, dizziness, undue fatigability and vague discomfort are known collectively as the syndrome of the trephined (ST). Both the symptoms of SSSF and ST are said to improve rapidly following cranioplasty. Therefore, this

leads to the hypothesis that the mechanism of onset for both the syndromes may be similar (Hodozuka *et al.*, 2000). It is the brain tissue compression as the result of lower intracranial pressure in the upright position and higher atmospheric pressure causing pressure gradient difference which acts on the cranial defect. Various theories on the pathophysiology of the syndrome have been described including a) direct cortical compression, b) hydrodynamically disturbed CSF parameters, c) hemodynamically reduced cerebral blood flow, cerebrovascular reserve capacity, and venous return as a result of pressure in the vasculature and brain tissue, d) disturbed metabolism. Besides that other known complications of DC include contralateral subdural effusions, infections (such as meningitis or brain abscess) and hydrocephalus. Persistent vegetative state is probably one of the most devastating outcomes following DC (Stiver, 2009).

Currently the main indications for cranioplasty are cosmetic reconstruction and cerebral protection. Cranioplasty is usually performed several months after DC with lack of specific guidelines on the timing of surgery. Unexpected improvements in patients neurological status has been observed in many centers. Suzuki *et al* reported five out of six patients actually showed improvement in neurological signs after cranioplasty (Suzuki *et al.*, 1993). These findings were also supported by Maekawa *et al* who reported improvement of neurological outcome in five of the eight patients post cranioplasty (Maekawa *et al.*, 1999). Till date the mechanism of improvement remains unclear. Yamamura *et al* in 1977 suggested that atmospheric pressure is transmitted to the cranial cavity through the cranial defect, causing inward rotation of the scalp (Yamamura and Makino, 1977). This pressure on the cranial defect can thus cause neurological deficit. The unprotected brain compression through the cranial defect by the atmospheric pressure can be normalized by cranioplasty (Wee and Kuo, 2014).

Improvement in cerebral perfusion after cranioplasty has since been established by many modalities. Yoshida et al in their studies using ^{133}Xe CT and ^{31}P magnetic resonance spectroscopy concluded that cranioplasty was able to improve cerebral blood flow and energy metabolism. Cerebral perfusion improvement after cranioplasty has also been shown by several other studies using trans-cranial Doppler (Winkler *et al.*, 2000; Chibbaro *et al.*, 2013; Wee and Kuo, 2014). More recently the use of CT perfusion imaging to measure CBF has been gaining popularity. This modality is generally easier to be performed and less operator dependent compared to transcranial Doppler and ^{133}Xe CT. Excellent cooperation from the patient is also needed if technique of measuring CBF is by using ^{133}Xe CT. Besides that, CBF measurement using CT perfusion gained much attention partly due to the improved helical scanning, CT scan machine and advances in the software used to analyse the data which aid in the accuracy and ease of performing (Sakamoto *et al.*, 2006). The procedure is also minimally invasive with only intravenous administration of iodinated contrast material. More importantly, CT perfusion has been validated and proven to have excellent correlation with ^{133}Xe CT in the measurement of CBF (Wintermark *et al.*, 2001). CT perfusion measurement of cranioplasty related perfusion changes were done by Sakamoto et al in 2006 and Sarubbo et al in 2014 (Sakamoto *et al.*, 2006; Sarubbo *et al.*, 2014)

In most neurosurgical center in Hospital Sungai Buloh and Malaysia, all patients that have undergone previous DC, will be treated similarly. All of the patients will eventually undergo reconstructive cranioplasty later, except for those with poor recovery (remained vegetative) or those who are elderly. The Department of Neurosurgery Hospital Sungai Buloh is the first in the country to be equipped with a brain suite that has been fully operational since the 10th of January 2011. CT perfusion imaging modality is available in the brain suite which enable intraoperative

perfusion mapping to be done. This study is done with the aim, to further establish the hypothesis that cranioplasty not only provides cerebral protection and cosmesis but also improve cerebral blood flow and clinical outcome.

CHAPTER TWO: LITERATURE REVIEW

DECOMPRESSIVE CRANIECTOMY

Decompressive craniectomy is used for management of various neurological emergencies (Brown *et al.*, 2008). This surgery is done by removing part of the skull to provide space for the injured and oedematous brain to expand and thus reducing intracranial hypertension. This is done to prevent the unavoidable sequelae of cerebral herniation in the event of uncontrolled intracranial hypertension. At the same time, cerebral perfusion can be improved (1996; Faul *et al.*, 2007).

Decompressive craniectomy is used for various conditions and commonly for traumatic brain injury, middle cerebral artery infarction and many others more. In 1901, Kocher reported the use of the large craniectomy for the treatment of cerebral oedema secondary to traumatic head injury which failed medical therapy (Kjellberg and Prieto, 1971). This technique was subsequently abandoned due to the high postoperative complication rate but is now widely used and has been the subject of numerous positive published series.

It is undeniable that DC has become widely accepted in the management of severe traumatic head injury. However, such a major procedure is not without its own list of complications. Most papers have concentrated on treatment of intracranial hypertension and outcome and relatively few have detailed the complications of the decompressive procedure (Yang *et al.*, 2008; Honeybul *et al.*, 2009). Among the complications known are such as surgical wound infection, herniation through the craniectomy defect, subdural/subgaleal effusion, syndrome of the trephined (ST), hydrocephalus, post traumatic seizures, hydrocephalus and rarely mortality (Honeybul and Ho, 2011).

The role of DC remains an unanswered question and has yet to be clearly defined if one considers the benefit and risk that comes with the procedure. What is less certain is whether there comes a point where the benefit of lowering the intracranial pressure outweighs the morbidity of surgery and therefore contributing to the improvement in patient's clinical outcome (Brown *et al.*, 2008).

CRANIOPLASTY

History:

History of cranioplasty dates back to 7000 B.C. (Shah *et al.*, 2014). In current modern neurosurgical practice patients who survived a DC will eventually require a cranioplasty, except in those who remained vegetative or elderly. However, many recent literatures regarding cranioplasty are based on case series that emphasize on the technical aspects of the procedure with minimal emphasis on clinical outcomes and perioperative complications of the procedure. Archeologic findings show that cranioplasty using inorganic materials started way before the use of organic materials. Beginning from the 19th century, the use of autologous bones from various donor sites such as the ribs and tibia, has gained wide popularity along with the use of other materials such as titanium and methyl methacrylate.

Materials of cranioplasty:

The choice of implant material for cranioplasty has long been controversial with no concrete evidence to suggest which is superior. Either alloplastic material or an autogenous bone has been used for reconstructive cranioplasty. Alloplastic materials are popular for uncomplicated primary

cranioplasty as it requires no donor site morbidity and has no complications related to donor site (Lee *et al.*, 1995). However, it acts as a permanent avascular foreign body and therefore contraindicated in problematic recipient beds such as dirty or infected wounds. Among the most frequently used alloplastic materials are hydroxyapatite cements, acrylics, titanium and carbon fiber-reinforced plastics (van Putten and Yamada, 1992). On the other hand, fresh autogenous bone reconstruction has been advocated because of its ability to become incorporated as living tissue with reparative capabilities. In comparing autologous bone kept in abdominal subcutaneous plane with the ones kept in tissue bank, there was no statistical difference between the two groups (Cheng *et al.*, 2014). The similar studies also showed where bone is kept in the tissue bank, the operation time and mean estimated blood loss was significantly less compared to those with bone kept in the abdominal wall.

An ideal cranioplasty material must have the following features (Blake, 1994):

- It must fit the cranial defect and achieve complete closure
- Radiolucency
- Resistance to infections
- Not dilated with heat
- Strong against biomechanical processes
- Easy to shape
- Not expensive
- Ready to use
- At present, there is still no perfect material to fit all these criteria.

Timing:

An optimal time of cranioplasty following craniectomy is intensely debated and inconclusive. Many studies showed no difference in terms of outcome when cranioplasty is performed at less than 12 weeks, 12-24 weeks and more than 24 weeks. Basheer et al showed that even though the differences were not statistically significant, patients who underwent cranioplasty after 24 weeks had more complications compared to the other 2 groups. However, in another study, the time of cranioplasty in between 16 to 20 weeks was shown to carry the highest risk of complications (Piedra *et al.*, 2014).

Complications:

The incidence of complications after cranioplasty varies and has been reported to range from 12% to 50% (Moreira-Gonzalez *et al.*, 2003; Matsuno *et al.*, 2006). Cranioplasty failure manifests with poor aesthetic results and inadequate cerebral perfusion. The overall complication rate is high, as reported by various studies (Sorensen *et al.*, 2003). As reported by Walcott et al, the complication rate of 23.8% was noted in a retrospective analysis to identify all complications related to cranioplasty and the influence of specific risk factors on the infection rate (Walcott *et al.*, 2013). Among the complications reported were hematoma, wound healing disturbance, surgical site infection, hydrocephalus, seizure and death.

Implant infection is the leading cause to cranioplasty failure. This risk can be minimized by securing a well vascularized, soft tissue cover, sealing any communication with the paranasal sinuses. A previously infected bed should be left to mature and confirmed clearance of bacterial foci, before any cranioplasty is to be carried out. After a routine cranioplasty, a 4-5% incidence of infection has been reported (Rish *et al.*, 1979). However, patients with a history of infection

have an up to eight-fold increased risk of reinfection with subsequent cranioplasty. When surgery was delayed longer than 1 year, the incidence of infection approached that of routine cranioplasty.

SYNDROME OF SINKING SKIN FLAP

The syndrome of ‘trephined’ (ST) or the syndrome of ‘sinking skin flap’ (SSSF) was first reported by Yamaura in literature in the year 1977 (Yamaura *et al.*, 1977). It is characterised by symptoms such as headache, epileptic seizures, vertigo, dysesthesias or paresis, which happens following extensive decompressive craniectomy.

Many attempts have been made to try to explain the pathophysiology of this condition. Previously it was believed that atmospheric pressure is directly transmitted to the intracranial cavity, causing an inward shifting of the scalp over the craniectomy site (Kwon *et al.*, 2012). However recently it has been proposed that a negative gradient between atmospheric and intracranial pressure, which is aggravated by changes in the CSF compartment following CSF hypovolemia to be the mechanism of neurological deterioration after craniectomy (Akins and Guppy, 2008).

The goal of treatment in syndrome of sinking skin flap is to restore the pressure exerted by depression of the craniectomy site (Schwab *et al.*, 1998). According to the Monro-Kellie’s Law, there is a reciprocal relationship between the volumes of brain tissue, blood and CSF which assures the equilibrium in the intracranial contents. Therefore, it is important to establish a physiological relationship between the brain structures in order to reinstitute a normal intracranial condition after cranioplasty. This can be achieved by injection of physiological

saline solution to replace the 'lost' quantity of ventricular CSF (Stula, 1982). Conservative management of sinking skin flap syndrome with neurological deterioration is largely ineffective. Cranioplasty is the principal surgical treatment that could improve the neurological deficits by a decrease in local intracranial pressure, and correction of abnormal CSF dynamics with subsequently reversal of symptoms (Sakamoto *et al.*, 2006).

NEUROPSYCHOLOGICAL ASSESSMENTS

Improvement in clinical outcome following reconstructive cranioplasty has been observed in the past. A 57 year old female presented with gait disturbance and poor activity who was diagnosed with SSSF was reported to recover well 2 weeks after cranioplasty (Sakamoto *et al.*, 2006). Various studies have used the Glasgow outcome scale (GOS), frontal assessment battery (FAB) and mini mental state examination (MMSE) for the evaluation of the neurology and cognition of patients undergoing cranioplasty after craniectomy. All these are bedside evaluations which can be carried out easily within a few minutes. A study carried out to evaluate impact of early cranioplasty on CBF and metabolism and its correlation with neurological and cognitive outcome concluded that 91% of its patients showed a clear and remarkable neuro-cognitive improvement tested by GOS, FAB and MMSE in the post-cranioplasty period (Chibbaro *et al.*, 2012). A similar study was repeated in 2013 also showed corresponding findings with statistically significant neurological and cognitive improvement was observed in 92% of patients following cranioplasty following assessment with the above tests (Chibbaro *et al.*, 2013).

Glasgow Outcome Scale (GOS)

The GOS was originally described in 1975. It is now widely used for classification of outcome of patients with traumatic brain injury whereby it is used by both acute care and rehabilitation specialists to assess recovery (Jennett and Bond, 1975). It is a multi-dimensional scale which assesses 5 categories: dead, vegetative (cannot interact, unresponsive), severely disabled (can follow commands, cannot live independently), moderately disabled (can live independently, reduced work capacity) and good recovery (can work) (Jennett *et al.*, 1977). The outcome is further divided into poor outcome (dead, vegetative and severely disabled) and good outcome (moderately disabled and good recovery). However it was noted that the original GOS is insensitive to small changes in functional status which are clinically relevant (James W, 2012). The extended version separates each of the three higher function categories into two, making eight categories in total (Heiskanen and Sipponen, 1970). Due to its popularity, the GOS remained widely used in multiple studies for assessment of patient's functional status post craniectomy and cranioplasty.

Mini Mental State Evaluation (MMSE)

The MMSE is used to assess cognitive function in neurology. As a detailed assessment of cognition is time consuming and requires a high standard of specialty, it is desirable to have a standardised simple and quick test to be routinely used (Dick *et al.*, 1984). Thus the MMSE was designed for a quick and accurate assessment. It is a quick test which takes approximately seven minutes to complete (Royall *et al.*, 1998). Despite its simplicity, it is able to test a broad range of cognitive functions which include orientation, recall, attention, calculation, language orientation,

recall, attention, calculation, language manipulation and constructional apraxia (Zarina ZA, 2007). The MMSE is shown to have a good reliability and validity among patients in the United States. However, problems can arise if it is used in a language other than English. The validity may be doubtful in a different cultural setting, especially where literacy is low (Kua and Ko, 1992). It also fails to identify executive dysfunction if it is quite severe (Angela J, 2002). This is because these groups of patients can still have a normal MMSE score but have severe functional limitations.

Even though the MMSE has been widely used to assess psychiatric patients, it has also gain its popularity among neurosurgical patients. The Koreans have used this test to assess the cognitive function among neurosurgical patients with various cerebral pathologies and treatments in an outpatient clinic. It has also been used to assess the cognitive function of patients with traumatic brain injury who underwent neurosurgical interventions. In Malaysia, the English version of MMSE was found not suitable due to language barrier and culture differences. Thus it was translated into the Malay language using the forward and backward translation method and was tested among 185 patients selected from 8 old folks home across Malaysia (Zarina ZA, 2007). This was the first study that translated the MMSE into the Malay language. Another validation study was done in 2009 among Malay speaking elderly population in Malaysia (Ibrahim *et al.*, 2009).

Frontal Assessment Battery (FAB)

The diagnosis and prognosis of brain diseases such as frontotemporal dementias and the severity of brain injuries can be accessed via the frontal lobe function (Dubois *et al.*, 2000). However, the

function of the frontal lobe can be difficult to be assessed clinically. It controls conceptualization and abstract reasoning, lexical verbal fluency and mental flexibility, motor programming and executive control of action, self-regulation and resistance to interference, inhibitory control and environmental autonomy. A bedside test called the frontal assessment battery was designed to specifically assess the frontal lobe function. It consists of six neuropsychological tasks which were pioneered by Luria, Lhermitte, Pillon and Serdaru (Kopp *et al.*, 2013) . Since then, the FAB has become increasingly popular for a variety of application in neurology, most notably the early diagnosis of neurodegenerative dementing diseases. A validation study was performed with patients suffering from different degenerative disorders known to involve the frontal lobes and showed that the FAB is a sensitive tool for these conditions (Appollonio *et al.*, 2005). It has also been used to assess the cognitive outcomes and activity of daily living among neurosurgical patients with intrinsic brain injury, whereby it showed satisfactory discriminating power.

CEREBRAL PERFUSION CHANGES WITH CRANIOPLASTY

Ever since improved neurological and functional outcome has been noted following reconstructive cranioplasty, various theories have been postulated for the phenomenon. Impairment of cerebral perfusion by means of cerebral blood flow was postulated as one of the mechanism seen in SSSF (Yamaura and Makino, 1977). Few studies in the past were done to evaluate the impact of cranioplasty on cerebral blood flow.

Improvement in dynamics of cerebral blood flow and metabolism in patients with cranioplasty was published back in 1996 (Yoshida *et al.*, 1996). Yoshida et al was able to demonstrate post-cranioplasty bilateral increase in CBF by using ^{133}Xe CT. Improved middle cerebral artery blood

flow velocity was noted in the operative hemisphere and contralateral hemisphere 7 days after cranioplasty in a study done by Winkler *et al.* He used transcranial Doppler ultrasonography to assess the difference in middle cerebral blood flow velocity between pre and post-cranioplasty (Winkler *et al.*, 2000). Similar findings of improved middle cerebral blood flow velocity on both hemispheres were also found in few studies done later, to further support this claim (Chibbaro *et al.*, 2012; Chibbaro *et al.*, 2013; Wee and Kuo, 2014).

More recently assessment of CBF using CT perfusion is gaining popularity due to the fact that it is less cumbersome to be performed and doesn't require high patient cooperation. It only involved simple intravenous contrast administration. Besides that, the advancement in helical scanning, CT scan machine and advances in the software used to analyze the data contribute to the accuracy in this modality. Single validation study has also been carried out to suggest the good correlation between CT perfusion and Xe CT (Wintermark *et al.*, 2001). Sakamoto *et al.* reported a case of improved CBF using CT perfusion in a patient with SSSF after undergoing cranioplasty (Sakamoto *et al.*, 2006). Improvement in clinical outcome and CBF assessment using CT perfusion and transcranial Doppler was also demonstrated by Chibbaro *et al.* in his study (Chibbaro *et al.*, 2013). In that study, 24 patients undergoing craniectomy for severe head injury were evaluated after cranioplasty and statistically significant brain perfusion improvement was seen at 6 weeks follow up predominantly in the ipsilateral hemisphere. Another study also showed increment of CBF using CT perfusion 7 days after cranioplasty in stable traumatic brain injury patients (Sarubbo *et al.*, 2014). However, in this study a drop in CBF was documented at 3 months post-cranioplasty. The reason behind this finding was speculated to be due to the restoration of flow compatible with prevailing metabolic demand rather than worsening perfusion.

CHAPTER THREE: OBJECTIVES

3.1 General objective

The objective of this study is to evaluate between pre and post-cranioplasty CBF and clinical outcome and to correlate CBF with clinical outcome in patients with previous decompressive craniectomy undergoing cranioplasty.

3.2 Specific objectives

The specific objectives of this study are as follows:

1. To evaluate pre and post-cranioplasty (1 day prior and 6 weeks post-cranioplasty) CBF by CT perfusion scan in the ipsilateral and contralateral hemispheres.
2. To evaluate pre and post-cranioplasty (1 day prior, 6 and 24 weeks post-cranioplasty) clinical outcome by Glasgow outcome score (GOS), Frontal assessment battery (FAB) & mini mental state examination (MMSE) scores.
3. To correlate post-cranioplasty (6 weeks post-cranioplasty) CBF with clinical outcome.

3.3 Research questions

1. Is there improvement in CBF between pre and post-cranioplasty (1 day prior and 6 weeks post-cranioplasty) in ipsilateral and contralateral hemispheres?

2. Is there improvement in clinical outcome by GOS, FAB and MMSE scores between pre and post-cranioplasty (1 day prior, 6 and 24 weeks post-cranioplasty)?
3. Is there any correlation between post-cranioplasty CBF and clinical outcome?

3.4 Null Hypothesis

1. There is no difference in CBF between pre and post-cranioplasty (1 day prior and 6 weeks post-cranioplasty) in ipsilateral and contralateral hemispheres
2. There is no difference in GOS, FAB and MMSE scores between pre and post-cranioplasty (1 day prior, 6 and 24 weeks post-cranioplasty)
3. There is no correlation between post-cranioplasty CBF with clinical outcome

CHAPTER FOUR: METHODOLOGY

4.1 Study design

This is a prospective observational study on patients who have underwent decompressive craniectomy for intracranial hypertension requiring reconstructive cranioplasty at Hospital Sungai Buloh from the period of 1st September 2013 to 1st September 2014.

4.2 Reference and source population

All patients aged over 18 and up to 65 years who underwent decompressive craniectomy for intracranial hypertension and requiring reconstructive cranioplasty at Hospital Sg Buloh from 1st September 2013 to 1st September 2014. They must also fulfill the inclusion criteria.

4.3 Sampling frame and data collection

Prior to recruitment, patients who underwent decompressive craniectomy for intracranial hypertension regardless of initial diagnosis and requiring reconstructive cranioplasty will undergo a face to face interview with their doctors in the clinic. Patients/Guardians will be informed regarding the nature of the study.

It will be emphasized that there will be no change in their management or treatment for their primary condition regardless of their participation in this study. Having obtained their verbal consent, patients will be screened for eligibility. Once screening for

eligibility is completed, a written informed consent will be obtained from the patient (if applicable) and guardian, before they are enrolled in this study.

4.4 Selection criteria

The inclusion criteria are as follows:

- I. Patients over 18 and up to 65 years
- II. Patients underwent decompressive craniectomy for intracranial hypertension regardless of initial diagnosis (eg: severe head injury, subarachnoid hemorrhage, intracerebral hemorrhage, venous sinus thrombosis, malignant middle cerebral artery, tumor etc)
- III. Patients undergoing reconstructive cranioplasty
- IV. Patients/Guardian informed about the study and giving consent

The exclusion criteria are as follows:

- Patients age <18 or >65 years
- Patients with previous bilateral decompressive craniectomy
- Patients allergic to CT contrast products
- Pregnant and nursing woman

4.5 Study schedule

All patients that were included in this study must first have an informed consent which fulfilled the requirement and reviewed by the Medical Research & Ethics Committee, Ministry of Health Malaysia (NMRR-12-1366-13599). The patient will then undergo a study schedule as follows:

4.5.1 Screening visit (during clinic follow up)

- I. Obtain both subject's and guardian's signatures on study's informed consent form
- II. Only guardian's consent will be taken if subject is deemed unfit for informed consent
- III. In the event that patient reverted to mentally capable for informed consent during the course of this study, informed consent will also be taken from subject with the presence of a guardian.
- IV. Obtain demographic information, medical history, allergy history to determine eligibility based on inclusion/exclusion criteria
- V. Ask for date of last menstrual period and do urine pregnancy test if required
- VI. Perform medical examination to determine eligibility
- VII. Schedule CT perfusion and clinical examination date for subjects who are eligible for the study. Provide subjects with instructions needed to prepare for the admission

4.5.2 Admission (1-2 days prior to cranioplasty)

- I. Perform CT perfusion scan prior to cranioplasty
- II. Record clinical assessment (GOS, FAB, MMSE) prior to cranioplasty
- III. Subject will then proceed with cranioplasty as planned

4.5.3 Visit 1 (6 weeks post-cranioplasty)

- I. Perform CT perfusions scan
- II. Record clinical assessment (GOS, FAB, MMSE)

4.5.4 Visit 2 (24 weeks post-cranioplasty)

- I. Record clinical assessment (GOS, FAB, MMSE)

4.6 Study procedure and evaluations

4.6.1 CT perfusion evaluation

CTP analysis was performed using 40-slice CT scanner (SIEMENS, SOMATOM Sensation Open) using a 40-s long continuous (cine) scan. One hundred and twenty axial images were constructed with three 9.6mm thick sections which covered a total of 28.8mm from the level of foramen of Monro to the lateral ventricle. The CT scanner protocols were 80kV, 209mA, 1s per rotation and at zero degree gantry. The CTP scan was started with a 4s delay after the injection of 40ml of non-ionic contrast agent Iopamidol (BRACCO, Iopamiro 370) at a rate of 6ml/s with an infuser pump

(STELLANT, medrad). All CTP scans were analyzed with a software package using an imaging workstation (SIEMENS, Syngo multimodality workplace 2010A). CBF map was generated for each patient and was expressed in ml/min/100g. As shown in Figure 4.3 CBF were measure in 3 circular regions of interest (ROIs) at a size of 1cm^2 , manually drawn on the plain CT brain and averaged CTP images in the ipsilateral hemisphere and then automatically reflected onto the contralateral hemisphere in the midline. In each patient, the CBF were averaged to generate a single value for each hemisphere. Below was the summary of CTP technical protocol:

- I. Cerebral blood flow (ml/100g/min) is assessed by CT perfusion scan (1 day prior and 6 weeks post cranioplasty).
- II. CT scan with a 40-detector row scan (SIEMENS, SOMATOM Sensation Open)
- III. Workstation for image analysis (SIEMENS, Syngo multimodality workplace 2010A)
- IV. Scanning protocol:
 - a. 3 contiguous 9.6mm slices in the region of interest (ROI)
 - b. Continuous acquisition (cine) with 80 kVp and 209mA
 - c. Duration of 40s with 1rotation/s
 - d. Obtain 120 axial images 9.6mm thick

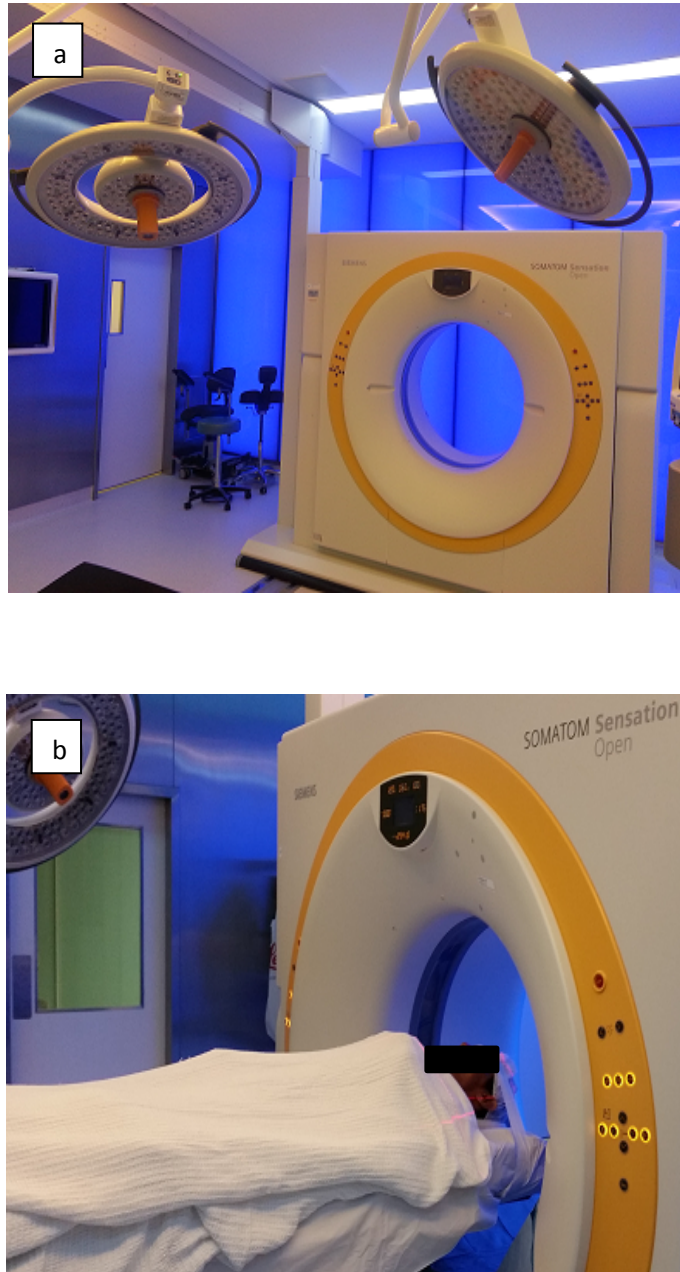


Figure 4.1: Patient undergoing CTP analysis performed using 40-slice CT scanner (SIEMENS, SOMATOM Sensation Open) (a,b)

V. Contrast media:

- a. At least 22-20G branulla
- b. Non-ionic contrast Iopamidol (Bracco, Iopamiro 370)
- c. 40ml of contrast with infusion rate of 6ml/s
- d. 50ml of Normal saline with infusion rate 6ml/s
- e. Time delay 4s from the beginning of the injection to the beginning of image acquisition

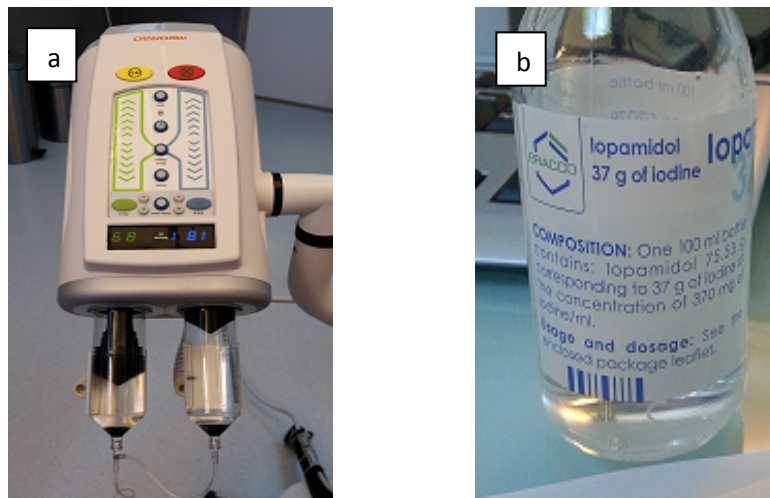


Figure 4.2 (a): 40-detector row scan (STELLANT, medrad), (b): Non-ionic contrast Iopamidol (Bracco, Iopamiro 370)